"DESIGN AND DEVELOPMENT OF FLOATING MICROSPHERE FOR H_2 ANTAGONISTS DRUGS"

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1. INTRODUCTION

1. Introduction

Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of Gastro-retentive floating microspheres Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micrometer. The Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs (Rajkumar K, 2012).

Microspheres are small in size and therefore have large surface to volume ratios. The concept of incorporating microscopic quantities of materials within microspheres dates back to the 1930s and to the work of Bungerberg de joing and co-workers on the entrapment of substances within coacervates. The potential uses of microspheres in the pharmaceutical have been considered since the 1960's and have a number of applications. The use of microspheres in pharmaceuticals have a number of advantages Viz., Taste and odor masking, conversion of oils and other liquids to solids for ease of handling, protection of drugs against environment (moisture, heat, light and oxidation), separation of incompatible materials, to improve flow of powders, production of sustained release, controlled release and targeted medications. The most important physico-chemical characteristics that may be controlled in microspheres manufacture are; particle size and distribution, polymer molecular weight, ratio of drug to polymer, total mass of drug and polymer Three decades, and various attempts have been done to retain the dosage form in the stomach as a way of increasing retention time (Rajkumar K, 2012)..

1.1 Advantages of Hollow Microspheres (Rajkumar K, 2012).

- Superior to single unit floating dosage forms as such microspheres releases drug uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.
- Improved receptor activation Selectivity
- Extended time over critical (effective) concentration
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.
- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in controlled manner for prolonged period.
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Extend patent protection, globalize product, and provide new business opportunities.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilize only in stomach.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.

1.2 Disadvantages (Rajkumar K, 2012).

- Drugs having irritant effect on gastric mucosa are not suitable candidates for FDDS.eg: NSAIDs, some antibiotics, digoxin, theophylline, corticosteroids, iron (ferrous sulfate), oral contraceptives, and tricyclic antidepressants.
- Drugs which are absorbed along the entire GIT and which undergo first pass metabolism may not be desirable e.g. nifedipine.
- They are not suitable candidates for drugs with stability or solubility problem in stomach.eg.ranolazine

- Single unit floating capsules or tablets are associated with an "all or none concept," but this can be overcome by formulating multiple unit systems like floating microspheres or microballoons.
- FDDS require sufficiently high level of fluid in stomach so that the system can float and thus sufficient amount of water (200- 250 ml) of water to be taken together with FDDS.

1.3 Suitable drug candidates for floating drug delivery system **(Kawatra M, 2012)**

Sustained release in the stomach is useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the In general, appropriate candidates for floating drug delivery system are the molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

- Drugs with narrow absorption window in GI tract, e.g., Para aminobenzoic acid, furosemide, riboflavin in a vitamin deficiency and Levodopa.
- Drugs which are primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, Chlordiazepoxide and Scinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g. Amoxicillin trihydrate.

1.4 FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS **(Narang N, 2011)**

a) Formulation factors

Size of tablets

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves. Floating and nonfloating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the nonfloating dosage units sank and remained in the

lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

Density of tablets

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities.

Shape of tablets

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened *in vivo* for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr.

Viscosity grade of polymer

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.

b) Idiosyncratic factors

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.

Posture

i) Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs

while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.

ii) Supine position

This position offers no reliable protection against early and erratic emptying. In supine subjects large dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant intake of drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time.

Feeding regimen

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins.

2. LITERATURE REVIEW

1. **Ramya Shivani B *et al* (2015)** was studied the Omeprazole loaded Floating microspheres by solvent evaporation technique. Total ten formulations was prepared by altering the concentration of drug to polymer concentrations. Process parameters such as stirring speed, stirring time and organic to aqueous phase ratio were optimized. Trials were made at 1:5 and 1:10 organic to aqueous phase ratio by altering drug to polymer concentration. Floating Microspheres were prepared by non-effervescent system. The obtained formulations were evaluated for drug content, entrapment efficiency, Buoyancy time and In vitro dissolution studies. The entrapment efficiency was found to be increased by increasing the concentration of the polymer. In vitro dissolution studies were conducted for a period of 12 hours. The drug release was continued up to 12 hrs with 99% drug release. From the study it was concluded that Formulation which has been prepared at 1:5 organic to aqueous phase ratio at 1:30 drug to polymer concentration was yielding the best floating microspheres which were floating for a period of 24 hrs.

2. **Pavan Kumar Perumandla *et al* (2014)** was studied the floating microspheres of Dextromethorphan hydrobromide (DXM HBr), which belongs to class antitussive. Floating microspheres was prepared for the improvement of bioavailability of Dextromethorphan hydrobromide by retaining in the stomach for prolonged period of time by solvent evaporation technique using polymers like ethyl cellulose (EC) and hydroxylpropyl methyl cellulose (HPMC K4M and K15M) in different ratios.The prepared floating microspheres were evaluated for micromeretic properities, percentage yield, *in vitro* buoyancy, drug entrapment efficiency, *in vitro* dissolution studies.

3. **Himansu Bhusan Samal *et al* (2011)** was studied the floating microspheres with Nateglinide as model drug for prolongation of gastric residence time. Nateglinide Floating Microspheres were prepared by w/o/o emulsification solvent diffusion technique using rate controlling polymers ethyl cellulose and hydroxy propyl methyl cellulose. The shape and surface morphology of prepared microspheres were characterized by optical and scanning electron microscopy respectively. FTIR

analyses the absences of drug-polymer interaction. In vitro drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of polymer concentration, solvent composition, particle size, drug entrapment efficiency and drug release were also observed. The prepared microspheres exhibited prolonged drug release (more than 12 h) and remained buoyant for > 24 h.

4. **Pandey Manisha *et al* (2010)** was studied the floating drug delivery system of famotidine. In the present study, preparation of famotidine floating microspheres, evaluation of Floating Drug Delivery System (FDDS) in vitro, prediction of the release, and optimization of stirring speed and polymers ratio to match target release profile was investigated. Floating microspheres were prepared by solvent evaporation (Oil-in-water emulsion) technique using hydroxylpropyl methylcellulose (HPMC) and Ethylcellulose (EC) as the rate controlling polymers. Particle size analysis, drug entrapment efficiency, surface topography, buoyancy percentage and release studies were performed. Results showed that the polymer ratio and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h), floating time (> 12 hr) and the best results were obtained at the ratio of HPMC:EC (1:6).

3. AIM AND OBJECTIVE

3.1 Aim

To design and develop floating microsphere for H_2 antagonist Drugs.

3.2 Objective

1. To provide prolonged and constant therapeutic effect.
2. To reduce the dosing frequency and therefore improve the patient compliance
3. To mask the taste and odor.
4. To provide controlled, sustained and targeted delivery of the drug.

4. PLAN OF WORK

4.1. Literature survey

4.2. Procurement of Drugs and Excipients

4.3. Preformulation study

4.4. Formulation of Floating Microsphere.

4.6. Evaluation of Floating Microsphere.

a) Micromeritic properties
    a. Tapped density
    b. carr'index
    c. hausner'ratio
    d. Angle of repose
b) Size, shape and Surface Analysis
c) Drug content
d) Buoyancy test
e) In-vitro drug release study
f) Stability Studies

4.7 Results and Discussion

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